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PHARMACOLOGY

# Observational, Prospective Single-Center Study of Antibiotic Prophylaxis with High-Dose Cefoxitin in Bariatric Surgery

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**ABSTRACT** The optimal dose of cefoxitin for antibiotic prophylaxis in obese patients remains uncertain. We evaluated the adequacy of a 4-g dosing regimen of cefoxitin against the most common pathogens that infect patients undergoing bariatric surgery. This observational prospective study included obese patients who required bariatric surgery and a 4-g dose of cefoxitin as an antibiotic prophylaxis. Serum concentrations were measured during surgery (incision, wound closure, and in case of reinjection). The pharmacokinetic/pharmacodynamic (PK/PD) target was to obtain free cefoxitin concentrations above 4× MIC, from incision to wound closure (100% *fT*>4×MIC). The targeted MIC was based on the worst-case scenario (the highest ECOFF value of *Staphylococcus aureus*, *Enterobacteriaceae*, and anaerobic bacteria). The secondary outcomes were the factors related to underdosage. A total of 200 patients were included. The mean age of the patients was 46 ± 12 years old, and the mean body mass index (BMI) was 45.8 ± 6.9 kg/m². Bypass surgery was the preferred technique (84%). The percentages of patients who met the PK/PD target (100% *fT*>4×MIC) of cefoxitin were 37.3, 1.1, and 0% for *S. aureus*, *Enterobacteriaceae* and anaerobic bacteria, respectively. BMIs below 50 kg/m² (odds ratio [OR] = 0.29, 95% confidence interval [CI] = 0.11 to 0.75, $P$ = 0.0107) and a shorter duration of surgery (OR = 0.97, 95% CI = 0.95 to 0.99, $P$ = 0.004) were associated with reaching the target concentrations. In obese patients undergoing bariatric surgery, a regimen of 4 g of cefoxitin led to an inadequate coverage for most common pathogens. A longer surgery duration and a BMI of >50 kg/m² increase the risk of underdosage. (This study was registered on ClinicalTrials.gov under identifier NCT03306290.)

**KEYWORDS** antibiotic prophylaxis, cefoxitin, obesity, pharmacodynamics, pharmacokinetics

Obesity is a public health and a pandemic problem according to the World Health Organization and represents a hug burden in terms of morbidity and mortality (1). Morbid obesity is associated with an increased risk of surgical site infection (SSI) (2). Among the factors implicated in SSI, antibiotic pharmacokinetic (PK) alterations are well described (i.e., increased renal and hepatic clearances and volume of distribution) (3, 4).

Bariatric surgery includes to two primary techniques, gastric bypass and sleeve gastrectomy (5), which have a reported SSI rate of 2% (2). Many risk factors have been shown to be associated with an increased SSI incidence after bariatric surgery, such as suboptimal dosing of antibiotic prophylaxis (AP) (6) or duration of surgery (7). In 2017, the French Society of Anesthesia and Critical Care Medicine recommended the use of

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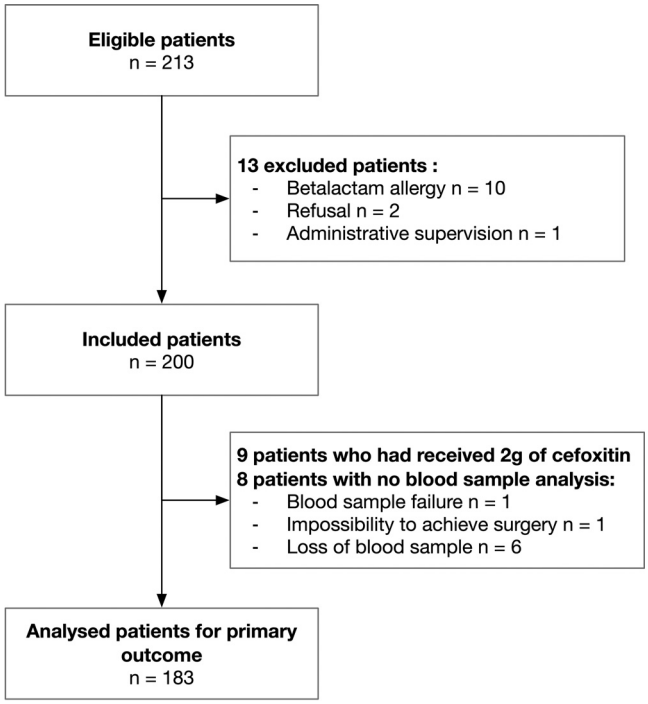


**FIG 1** Flowchart of the study.

cefoxitin as AP for bariatric surgery due to the increase of Gram-negative bacterial strains resistant to cefazolin and the activity of cefoxitin against anaerobic species (8). In addition, the dose of cefoxitin was recommended to be doubled in cases of total body weight greater than 100 kg or a BMI of $>35$ kg/m$^2$ to account for potential alterations in PK parameters described in this population. Cefoxitin is highly water soluble, as indicated by its low volume of distribution ($V$ = 0.1 to 0.2 liter/kg), including in patients with a body mass index (BMI) of $>40$ kg/m$^2$ (7). Cefoxitin is 70 to 80% protein bound and has a serum half-life of 0.75 h in adults with normal renal function (9).

Previous studies regarding the cefoxitin concentration used in the obese population for AP were small or varied in study design (6, 7, 10). Among the doses of cefoxitin that have been evaluated, 2 g was consistently associated with an underdosage (6, 10). One study, which involved the largest obese cohort to date (30 morbidly obese patients), determined the pharmacokinetics and pharmacodynamics (PK/PD) of a weight-based cefoxitin dosing regimen (40 mg/kg, based on total body weight). However, the design of this study cannot be extrapolated to daily routine practice. Moreover, the use of weight-based dosing is not yet a standard of care, and toxic effects of very high dose of $\beta$-lactams should be evaluated and considered. Thus, the aim of this pragmatic study was to elucidate whether a 4-g dose of cefoxitin leads to an adequate concentration against the most common pathogens in bariatric surgery during routine workflow.

## RESULTS

The flowchart of patient inclusion is presented in Fig. 1. A total of 213 patients were eligible, 200 patients were included, and 183 were finally analyzed for primary outcome. Overall, the mean age was 45 $\pm$ 12 years old, and most patients were women (75.6%). The mean BMI was 45.8 $\pm$ 6.9 kg/m$^2$. Regarding the type of surgery, 169 (84%) and 31 (16%) were gastric bypasses and sleeve gastrectomies, respectively. The mean duration of surgery was 93 $\pm$ 28 min. For 34 patients, the surgery duration exceeded 120 min. From the concentrations at incision and wound closure, half-life of cefoxitin was estimated at 2.18 $\pm$ 2.38 h. No adverse event was reported during the study. Table 1 describes the patients and surgery characteristics.

**TABLE 1** Patient characteristic data of the study cohort ($n = 200$)[a]

| Variable | Result |
|---|---|
| Demographic characteristics | |
| Female, no. (%) | 151 (75.5) |
| Mean age in yr (SD) | 45.6 (12.1) |
| Mean ht in cm (SD) | 166.3 (24.0) |
| Mean wt in kg (SD) | 126.4 (8.8) |
| Mean BMI in kg/m$^2$ (SD) | 45.5 (6.9) |
| Mean body area in m$^2$ (SD) | 2.50 (0.27) |
| Mean ideal body wt in kg (SD) | 60.7 (6.6) |
| Renal function | |
| Mean plasma creatinine in $\mu$mol/liter (SD) | 74.8 (59.0) |
| Mean plasma creatinine clearance in ml/min/1.73 m$^2$ (SD) | 88.9 (21.4) |
| Chronic kidney disease (<60 ml/min/1.73 m$^2$), no. (%) | 15 (7.5) |
| Surgery characteristics | |
| Type of surgery, no. (%) | |
| Gastric bypass | 169 (84.5) |
| Sleeve gastrectomy | 31 (15.5) |
| Abdominal access technique, no. (%) | |
| Laparoscopy | 182 (91) |
| Laparotomy | 2 (1) |
| Robot assisted laparoscopy | 16 (8) |
| Mean duration of surgery in min (SD) | |
| Bypass surgery | 95 (27) |
| Sleeve gastrectomy | 85 (29) |
| Mean vascular filling in ml (SD) | 766.9 (269.8) |
| Mean wt-adjusted vascular filling in ml/kg (SD) | 12.7 (4.8) |

[a]Quantitative continuous normal data are presented as means (with standard deviations [SD]), and nominal qualitative data are presented as numbers and percentages (%). The ideal body weight was calculated using the Lorentz formula. The body area was calculated using the Boyd formula. Chronic kidney disease was defined as creatinine plasma clearance calculated with an MDRD formula value of <60 ml/min/1.73 m$^2$. Weight-adjusted data were adjusted using the ideal body weight.

**Primary outcome.** The percentage of patients who met the PK/PD target (100% *fT*>4×MIC) of cefoxitin was 37.3, 1.1 and 0% for *S. aureus*, *Enterobacteriaceae* and anaerobic species, respectively (Table 2).

**Secondary outcomes. (i) Factors associated with underdosage.** In the bivariate analysis, factors associated with reaching the target concentration at wound closure were sex (female), age (older patients), lower glomerular filtration rate, a second injection of cefoxitin, a shorter (<2-h) surgery duration and type of surgery (Table 3). In the multivariable analysis, a BMI of <50 kg/m$^2$ (OR 0.29, 95% CI = 0.11 to 0.75, $P$ = 0.0107), the duration of surgery (OR = 0.97, 95% CI = 0.95 to 0.99, $P$ = 0.004), and sleeve gastrectomy surgery (OR = 2.94, 95% CI = 1.02 to 8.46, $P$ = 0.045) were associated with reaching target concentrations of cefoxitin for *Staphylococcus aureus*. A second injection of cefoxitin (if surgery exceeded 2 h) was associated with a signifi-

**TABLE 2** PK/PD target attainment in the CEFOBAR study population during bariatric surgery[a]

| | PK/PD target | | |
|---|---|---|---|
| Parameter | 16 mg/liter | 32 mg/liter | 64 mg/liter |
| % patients reaching the PK/PD target | | | |
| $C_1$>4×MIC | 91.7 | 27.4 | 1.2 |
| $C_3$>4×MIC | 37.5 | 0.6 | 0.0 |
| % dosing interval above the PK/PD target | | | |
| 100% *fT*>4×MIC | 37.3 | 1.1 | 0.0 |

[a]The primary outcome is expressed as a percentage of the dosing interval greater than 4× the MIC, the percentage of patients with cefoxitin concentrations greater than 4× the MIC. The percent dosing interval greater than 4× the MIC is expressed as the means ± the SD.

**TABLE 3** Factors associated with reaching target concentrations of *S. aureus* (>16 mg/liter) at the end of the intervention: bivariate regression and multivariate regression ($n = 183$)[a]

| Parameter | n | Bivariate regression | | | Multivariate regression | | |
|---|---|---|---|---|---|---|---|
| | | OR | 95% CI | P | OR | 95% CI | P |
| Gender | | | | 0.8775 | | | 0.3518 |
| Male | 45 | 1 | | | 1 | | |
| Female | 138 | 1.06 | 0.53–2.10 | | 0.66 | 0.28–1.58 | |
| Age* | 183 | 1.02 | 0.99–1.04 | 0.2033 | 1.02 | 0.99–1.05 | 0.2044 |
| BMI (kg/m²)* | 183 | 0.97 | 0.92–1.01 | 0.1692 | | | |
| BMI > 50 kg/m²* | | | | 0.0489 | | | **0.0107** |
| ≤50 | 140 | 1 | | | 1 | | |
| >50 | 43 | 0.47 | 0.22–1.00 | | 0.29 | 0.11–0.75 | |
| GFR, MDRD formula (ml/min/1.73 m²)* | 182 | 0.99 | 0.98–1.00 | 0.1828 | 0.99 | 0.97–1.00 | 0.0687 |
| Kidney failure (GFR < 60 ml/min/1.73 m²) | | | | 0.0751 | | | |
| No | 167 | 1 | | | | | |
| Yes | 16 | 2.62 | 0.91–7.54 | | | | |
| Fluid loading (ml)* | 183 | 1.00 | 1.00–1.00 | 0.9499 | | | |
| Surgery | | | | 0.4211 | | | **0.0450** |
| Gastric bypass | 157 | 1 | | | 1 | | |
| Sleeve gastrectomy | 26 | 1.84 | 0.80–4.23 | | 2.94 | 1.02–8.46 | |
| 2nd injection of cefoxitin (2 g) | | | | 0.0439 | | | **0.0005** |
| No | 167 | 1 | | | | | |
| Yes | 16 | 3.26 | 1.03–10.32 | | 21.69 | 3.83–122.8 | |
| Cefoxitin total dose | | | | 0.0246 | | | |
| 4 g | 167 | 1 | | | | | |
| 6 g | 16 | 3.54 | 1.18–10.66 | | | | |
| Surgery duration (min)* | 183 | 1.00 | 0.90–1.01 | 0.5968 | 0.98 | 0.96–0.99 | **0.0109** |
| Surgery duration and 2nd injection | | | | 0.0798 | | | |
| ≤120 min | 149 | 1 | | | | | |
| >120 min without 2nd injection | 18 | 1.03 | 0.38–2.80 | | | | |
| >120 min with 2nd injection | 16 | 3.55 | 1.17–10.75 | | | | |
| Delay between end of infusion and sampling | | | | 0.4910 | | | |
| Before the rend | 36 | 1 | | | | | |
| 0 to 15 min after the end | 111 | 0.89 | 0.41–1.90 | | | | |
| 15 to 30 min after the end | 23 | 0.90 | 0.31–2.62 | | | | |
| >30 min after the end | 13 | 2.24 | 0.61–8.21 | | | | |

[a]CI, confidence interval. *, quantitative variables have no reference level. The odds ratio (OR) expresses the risk variation for a unit increase of the variable. Factors reaching a threshold of 0.25 were candidates in a multivariable regression model for which the significance threshold of *P* values of <0.05 (boldface) in two-sided tests were considered significant. GFR, glomerular filtration rate.

cantly greater probability to reach the MIC objective (OR = 21.69, 95% CI = 3.83 to 122.8, $P = 0.0005$).

**(ii) Distribution of free cefoxitin concentrations.** At $T_1$ (incision), the mean *fC* in the serum was 26.3 (±9.9) mg/liter. At T3 (wound closure), the mean *fC* was 15.9 ± 8.3 mg/liter. At $T_2$ ($n = 16$), 30 min after reinjection, the mean *fC* was 30.8 ± 20.8 mg/liter. The entire distribution of *fC* is reported in Fig. 2. The percentages of patients who reached *fC*>4×MIC at each time point, regardless of the targeted pathogens, are reported in Fig. 3.

**(iii) Incidence of surgical site infection.** Of 183 subjects for whom the SSI assessments were available at day 30 after the surgery, three subjects (1.6%) developed an SSI, one of which was superficial (trocar infections) and two were organ/space SSIs (ileitis). Of these three patients, none reached any of the PK/PD objectives (100% *fT*>4×MIC). Microbiological identifications were not available for these patients (no

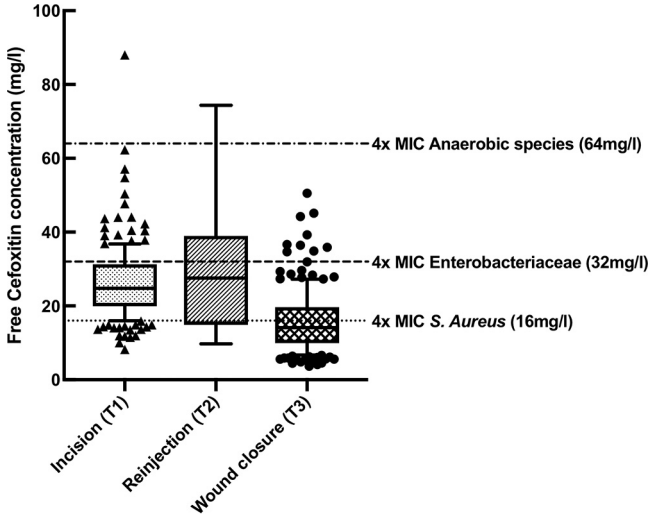


**FIG 2** Free cefoxitin concentration during surgery at each point. The data are presented as the medians, interquartile intervals (box plot), and 10th and 90th percentile deviations (error bars) with values above 90th percentile and below 10th percentile (black triangle for $T_1$ and black circles for $T_3$). The four time points for the MIC thresholds are presented for main bacterial species isolated in bariatric surgical site infections.

medical reasons for revision surgery or microbiological samplings). SSI diagnoses were made between 7 and 14 days after the surgery.

## DISCUSSION

In bariatric surgery, the use of a 4-g dose of cefoxitin ensured 100% *fT*>4×MIC in 37.3% of cases for the *S. aureus* coverage. For *Enterobacteriaceae*, the rate of 100% *fT*>4×MIC target attainment decreased to 1.1%. No patient had adequate coverage for anaerobic bacteria. A BMI of >50 kg/m² and a longer duration of surgery were significantly associated with an increased risk of underdosage. A decreased risk of underdosage was observed with a reinjection of 2 g of cefoxitin when surgery lasted more than 2 h and when sleeve gastrectomy was performed. Regarding SSI, we observed a similar rate compared to recent studies (1.6%) (29). This study describes the largest cohort of morbid obese patients undergoing bariatric surgery receiving cefoxitin as antibiotic prophylaxis.

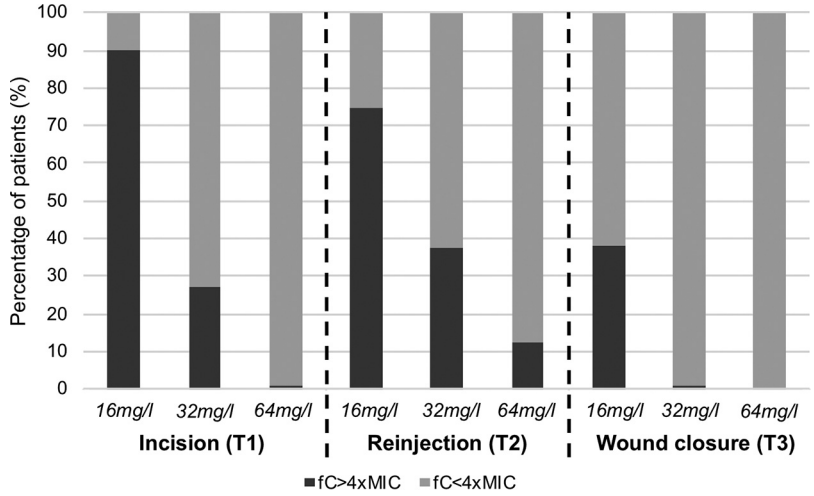


**FIG 3** Serum PK/PD attainment. *fC*>4×MIC is the cumulative free cefoxitin concentration above 4× the MIC at three time points; *fC*<4×MIC is the cumulative free cefoxitin concentration below 4× the MIC at three time points. The data are expressed as percentages.

Previous studies reported a risk of underdosage with cefoxitin use in various surgeries involving obese patients. A 2-g dose has been consistently associated with the occurrence of underdosage (6, 10), whereas the rate of target attainment with a 4-g dose limits the risk of underdosage without being optimal (7). In 2016, Moine et al. proposed a weight-based dose (40 mg/kg of total body weight), leading to a median dose of 5 g of cefoxitin. This higher dose was also inadequate for *Bacteroides fragilis* but was adequate for *S. aureus* and *Enterobacteriaceae*. Similarly, we observed a difference for the rate of target attainment for *S. aureus* versus other species. Nevertheless, our rate of target attainment was much lower than that previously described. This discrepancy can be explained by a different PK/PD objective. In contrast to previous studies, we considered the PK/PD target to be above 4× the MIC based on a worst-case scenario and not 1× MIC (7, 10). Likewise, the choice of 100% $fT>4\times$MIC instead of 70% was explained by the necessity of an adequate antibiotic coverage from incision to wound closure (11).

We acknowledged that it constitutes an aggressive PK/PD target. Indeed, this objective was recommended in order to attain the maximal bactericidal effect, which is reached for a concentration between 4 and 8× the MIC. Nevertheless, the objective of 4× the MIC was supposed to take into account the inaccuracy in the determination of the MIC (12) and in the measurement of plasma concentrations of $\beta$-lactams up to ±15% (13). Furthermore, tissue concentrations are inferior to serum concentrations, and the penetration of cefoxitin in the adipose tissue appeared to be very low (8%) (6, 7). For agents with a wide therapeutic range, such as the $\beta$-lactams, increased systemic doses can be a viable solution to achieve adequate tissue concentrations (14). Taken together, these results suggest that a higher target serum concentration of cefoxitin needs to be attained.

A BMI of >50 kg/m$^2$ was significantly associated with an increased probability of not reaching the PK/PD target for *S. aureus*. Previous studies concerning $\beta$-lactam (mostly cefazolin) PK/PD for AP in which BMIs were compared observed significant differences in plasma and/or tissue free concentrations of antibiotics (15–17). Concerning cefoxitin, BMI as a factor of underdosage was never specifically explored in these studies (6, 7). From a pathophysiological point of view, our results are supported by obesity-associated physiological changes, such as increased hepatic or renal clearance or increased cardiac output (3, 4).

Sleeve gastrectomy surgery was associated with an increased probability of reaching the PK/PD target. Compared to gastric bypass, the sleeve gastrectomy surgery is considered to be shorter and technically easier to perform, and it induces less surgical trauma to the tissue (5), although additional data are needed to confirm this tendency.

Similarly, longer duration of surgery was associated with an increased risk of underdosage. Previous studies have indicated that too short a duration of AP is associated with a higher risk of SSI (18). Similarly, we demonstrated the benefits of reinjection to limit the effects of an insufficient AP concentration at wound closure. Indeed, the dosage at wound closure was the most affected, and the reinjection could limit its occurrence. Among alternatives to limit the risk of underdosage, particularly in surgery exceeding 2 h, prolonged infusion could constitute a good option, as recently suggested (19).

Half-life values observed for cefoxitin in our study were higher than those determined in previous studies, ranging from 1.0 to 1.2 h (6, 7, 10). In the previous studies, the included obese patients had a normal renal function. Here, 9% of the patients presented with a moderate (or severe) renal insufficiency. Moreover, the sample size could have impacted the half-life value because of the interindividual difference.

No adverse event was noted with the dose of 4 g of cefoxitin. It was previously described that the risk of toxicity depended of multiple factors (age and comorbidities, such as renal insufficiency) (20). In this study, the population was mostly composed by young patients with normal renal function. Second, the duration of exposition rather that the dose itself seems to be associated with the emergence of neurotoxicity. In the case of surgical prophylaxis, the length of treatment should never exceed 24 h. Here, the cefoxitin was systematically interrupted at the end of the surgery.

We acknowledge that the estimation of the free concentration instead of a direct measurement could constitute a weakness of this study. We opted for the determination of cefoxitin total serum concentration because we did not have access to direct measurement of the free concentration. Nevertheless, the use of free concentration is still debated since it appears to be underestimated either as a result of drug adsorption during ultracentrifugation or by instability during dialysis (21–23). To the best of our knowledge, no study has evaluated the difference between the measured and estimated free fractions of cefoxitin. Data from Wong et al. suggested that significant differences exist between measured and estimated free drug concentrations for highly protein-bound $\beta$-lactams, such as ceftriaxone or flucloxacillin. In contrast, cefazolin, whose structure and properties are close to those of cefoxitin, has shown a limited bias (inferior to 10% overestimation) between the predicted and measured free concentration (21). Thus, the unbound cefoxitin fraction varies widely from 20 to 48% in the literature (24). In the worst-case scenario, we deliberately opted for the lowest free fraction because of the prophylaxis situation following the classification of surgical wound classification of Altemeier et al. (25). Bariatric surgery is considered a "clean-contaminated" procedure where antibiotic prophylaxis is indicated.

Among the potential limitations of our study, we did not perform fatty tissue concentration measurements. Whatever the actual methods of tissue dosage, microdialysis, or matrix-assisted laser desorption/ionization mass spectrometric imaging, these techniques must be implanted surgically and are time-consuming. Thus, during routine workflow, both methods would be difficult to obtain for 200 patients. Finally, to our knowledge, there are no robust data regarding the optimal technique for both sampling and measurement (14).

This study, encouraged by previous data, investigated the optimal PK/PD target that should be reached. Indeed, despite a very low rate of target attainment, the incidence of SSI in bariatric surgery remains low. However, no study has evaluated the impact of underdosage on a hard clinical endpoint such as SSI. In addition, the occurrence of SSI is not only related to the quality of AP but also depends on other factors, such as the duration of surgery or the length of hospitalization, which also need to be considered. Currently, several ongoing studies are evaluating the optimal PK/PD target for curative strategies. To the best of our knowledge, there is no equivalence in the context of surgical prophylaxis. Thus, the definition of the PK/PD objective (total versus free concentration, MIC objective) for AP, especially in a specific population such as obese patients, is urgently needed.

**Conclusions.** In obese patients undergoing bariatric surgery, a regimen of 4 g of cefoxitin led to inadequate coverage for most common pathogens. The low rate of SSI associated with this surgery requires the PK/PD target to be defined for surgical prophylaxis.

## MATERIALS AND METHODS

**Study design.** This was a single center prospective observational study conducted at the University Hospital of Nancy, France, tertiary center (Centre Specialisé Obésité [CSO] network) in bariatric surgery (>400 procedures/year, four dedicated bariatric surgeons), between 1 November 2017 and 9 August 2018. The CEFOBAR (CEFOxitin for BARiatric surgery) protocol was reviewed and approved by the Patient Protection Committee SUD-EST IV (IDRCB 2017-A01285-48). All eligible patients provided written informed consent before inclusion in the study.

This study was registered on ClinicalTrials.gov under identification number NCT03306290. This manuscript was written in accordance with the STROBE statement (www.strobe-statement.org) for the reporting of observational studies.

**Inclusion and exclusion criteria.** Obese patients (defined as having a BMI of >35 kg/m$^2$), age 18 years and older, scheduled for elective bariatric surgery (gastric bypass or sleeve gastrectomy) were eligible. Exclusion criteria included a known history of an allergy to $\beta$-lactam antibiotics and declining to consent.

**Study protocol.** Cefoxitin was prescribed and administered as part of the routine anesthesiology care. Prescriptions followed the French Society of Anesthesiology and Critical Care Medicine guidelines (8): a dose of 4 g of cefoxitin administered by intravenous infusion 30 min before the surgical incision is recommended, and a second 2-g dose is administered if the surgery time exceeds 2 h. In the case of a total body weight below 100 kg, a 2-g dose of cefoxitin is recommended.

Patients underwent routine general anesthetic induction and maintenance. Antibiotic administration was discontinued at the end of surgery.

Serum samples were collected at three time points: incision ($T_1$), wound closure ($T_3$), and 30 min after a reinjection, if indicated ($T_2$).

**Cefoxitin analysis of serum.** The serum samples were withdrawn from the forearm opposite the arm used for cefoxitin infusion. The samples were collected in tubes with no additives (BD Vacutainer serum tubes; Becton Dickinson, Le Pont de Claix, France) and immediately stored at 4°C. Samples were prepared according to a method involving precipitation and purification using acetonitrile and chloroform. After centrifugation at 10,000 × *g* for 10 min, the supernatants were injected into a chromatographic system (Thermo Finnigan Spectra system HPLC coupled with a photodiode array UV detector [UV6000LP Thermo Finnigan, Courtaboeuf, France]) using an Atlantis T3 analytical column (150.0 by 4.6 mm, 5 $\mu$m; Waters, Saint Quentin, France) coupled with an Atlantis T3 guard column (2.0 by 4.6 mm, 5 $\mu$m; Waters, Saint Quentin, France). The detection of total cefoxitin was performed at 260 nm. Quantification of cefoxitin was performed using an external standard calibration with a lower and upper limits of quantification at 1 and 400 mg/liter, respectively. The repeatability and the intermediate precision of the chromatographic method were lower than 10 and 15%, respectively.

The percentage of the free fraction of cefoxitin ranged from 20 to 48% (24). Since AP is based on the worst-case scenario, the lowest free fraction of 20% was chosen. The distribution of the total cefoxitin concentration (measured) and the free cefoxitin concentration (estimated) was reported.

**Data collection.** Patient baseline characteristics and SSI variables were collected using a standardized form from the electronic patient medical record. The baseline characteristics collected at hospital admission were age, gender, comorbidities, BMI, baseline serum creatinine, glomerular filtration rate (calculated using the MDRD formula), and the type and duration of surgery. Regarding AP, the time of cefoxitin injection and time of serum sample collection were collected. The half-life of cefoxitin was calculated. The perioperative fluid intake was recorded. The occurrence of adverse events related to cefoxitin was recorded during the hospitalization. The SSI was defined according to the proposed criteria of the Centers for Disease Control and Prevention (26).

**PK/PD target.** The PK/PD target was defined as a free concentration above 4× the MIC (based on European Committee on Antimicrobial Susceptibility Testing [EUCAST] epidemiological cutoff values [ECOFF]). Antibiotic prophylaxis for bariatric surgery should target the following bacteria: *Staphylococcus aureus*, *Enterobacteriaceae*, and anaerobic bacteria (27). Based on an $MIC_{90}$ for cefoxitin obtained from the EUCAST (28), adequate concentration was defined as a free cefoxitin serum concentration (*fC*>4×MIC) above 16, 32, or 64 mg/liter for *Staphylococcus* (MIC of 4 mg/liter), *Enterobacteriaceae* (MIC of 8 mg/liter), and anaerobic bacteria (MIC of 16 mg/liter), respectively.

The dosing interval was defined as the time between incision and wound closure (here between $T_1$ and $T_3$) (11). The 100% time > 4× the MIC (100% *fT*>4×MIC) was defined as a cumulative free cefoxitin concentration greater than 4× the MIC at three time points.

**Outcomes.** The primary outcome was the percentage of patients who met the PK/PD target at 3 time points (100% *fT*>4×MIC). Secondary outcomes were also investigated. Factors known to be associated with changes in the PK/PD target, such as age, gender, BMI, glomerular filtration rate, duration of surgery, and intraoperative fluid loading, were analyzed. The *fC*>4×MIC at each time point was described. At each time point, the percentages of patients who reach *fC*>4×MIC regardless of the targeted pathogen were determined. Finally, the surgeons recorded prospectively the occurrence of SSI within 30 days after surgery during the routine postoperative follow-up.

**Sample size calculation and statistical analysis.** Based on previous studies evaluating the cefoxitin concentration and the PK/PD target of a free cefoxitin concentration greater than 4× the MIC, we hypothesized that the free cefoxitin concentration at the end of the surgery would be <64 mg/liter (4× the highest MIC, i.e., 16 mg/liter for anaerobes, worst-case scenario) in approximately 50% of the patients. A sample size of 200 patients was needed to study the effect on target serum concentrations of approximately 10 variables. Descriptive statistics were used to assess the characteristics of the included patients and surgery, as well as the free cefoxitin serum concentrations at the surgical incision, including at 30 min after the second injection (when appropriate) and at the end of the surgery. Continuous variables are presented as means and standard deviations (SD), and categorical variables are presented as percentages.

Statistical analysis was a per-protocol analysis restricted to patients who received 4 g of cefoxitin. In order to obtain a homogenous population, only patients who received 4 g of cefoxitin were analyzed for the primary and secondary outcomes.

The characteristics of the patients and the surgery associated with reaching the target blood concentration, considering an MIC of 4 mg/liter (i.e., free serum concentration > 16 mg/liter), at the end of the surgery ($T_3$) were identified using a bivariate logistic regression model. Factors reaching a threshold of 0.25 were then candidates in a multivariable regression model for which the significance threshold *P* values of <0.05 in two-sided tests were considered significant. The variable "cefoxitin total dose" was not introduced in the model because of high colinearity with the variables "second injection of cefoxitin." Missing values were not imputed, and patients with missing variables were excluded from the analyses.

The risk of bias is considered to be limited due to the large number of patients included in this pharmacological study. A limited number of patients will be lost since they all had intensive medical and surgical follow-up, especially regarding the risk of surgical site infection. The logistic regression results are expressed as crude (bivariate model) and adjusted (multivariable model) odds ratios (OR), their 95%

confidence intervals (CI), and *P* values. No interim analysis was performed. All analyses were performed by an independent biostatistician using SAS v9.4 (SAS Institute, Inc., Cary, NC).

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